REMARKS

Status of the claims

Claims 1-52 were originally presented for examination. The claims were restricted into three groups in an Office Action dated July 1, 2004. In a Response dated July 29, 2004, Applicants elected Group II (polynucleotides encoding zinc finger binding proteins, vectors and host cells), with traverse, and canceled claim 29. The elected group included originally presented claims 30-32 and 39-41 and amended claims 2-28 and 34-38. Accordingly, claims 1-28 and 30-52 were pending and claims 2-28, 30-32 and 34-41 were under consideration.

By virtue of this response, claims 1, 6, 10, 28, 30, 38, 39, 42, 48 and 52 are amended and new claim 53 is added. Exemplary support for the amendments to independent claim 30 is found as follows:

non-canonical zinc finger component: page 4, lines 1-14
page 6, lines 14-16

beta turn comprising the two amino-terminal zinc coordinating residues and alpha helix comprising the two carboxy-terminal zinc coordinating residues:
page 1, lines 25-30
page 2, lines 18-19
page 7, line 10
page 17, line 20 through page 18, line 2

zinc-coordinating residues do not consist of two cysteine residues and two histidine residues: page 1, lines 25-30
page 7, line 19 through page 8, line 4
p. 19, line 14 through p. 20, line 15

engineered to bind to a target sequence: page 10, lines 17-29
page 18, line 18 through page 19, line 2

Support for the amendment to claims 38 and 48 is found in the material written into the paragraph beginning at page 23, line 28 (by amendment herein), incorporated by reference (*see, e.g.*, page 23, lines 28-29 of the present specification) from WO 01/41566. Support for the amendment to claim 42 is found, for example, at page 25, line 28 through page 26, line 3 and page 28, line 12 through page 29, line 21. Applicants submit that new claim 53 is a member of elected group II and support therefor is found at page 6, lines 20-27 of the specification.

Thus, following entry of this response, claims 1-28 and 30-53 will be pending and claims 2-28, 30-32, 34-41 and 53 will be under consideration. *See* also the section entitled "Restriction and Species Election" below.

Specification

The specification has been amended on page 1 to correct a typographical error. The specification has been amended on page 23 to write in material incorporated by reference from WO 00/41566 (as stated, for example, at page 23, lines 28-29 of the present specification) corresponding to page 30, lines 18-26 and page 33, lines 6-19 of WO 01/41566.[1] The same paragraph has also been amended to replace the serial numbers of U.S. provisional patent applications with the publication numbers of their corresponding International Patent Applications. No new matter is added.

Restriction and Species Election

As noted above, Applicants believe that claims 2-28, 30-32, 34-41 and 53, conforming to elected Group II, are presently under consideration. The Office Action states that claims 1, 3, 5, 7-9, 11-21, 23, 24, 33-35, 38 and 42-52 have been withdrawn. Applicants note that, although claims 3, 5, 7-9, 11-21, 23, 24, 33-35 and 38 have not yet been considered, they are not withdrawn as the result of a Restriction Requirement.

[1] It is noted that WO 01/41566 corresponds to U.S. Patent No. 6,534,261

Rather, because they recite non-elected species, they will be considered upon allowance of a generic claim.

Moreover, Applicants believe that presently pending claim 30 is a linking claim, linking the proteins of Group I (which are encoded by the polynucleotides of group II) with the methods of group III (which utilize the polynucleotides of Group II).

Applicants also note that method claims 42-51 have been amended to recite all of the limitations of independent claim 30; accordingly, Applicants reserve their right to rejoinder of claims 42-51 upon allowance of the product claims currently under consideration.

Although not explicitly stated in the Office Action, Applicants assume the Restriction Requirement has been made final. Applicants maintain traverse, and reserve their right to petition the finality of the Restriction Requirement.

35 U.S.C. § 112, second paragraph

Claims 10, 28, 36, 37, 39, 40 and 41 stand rejected as allegedly indefinite.

Claim 39 was stated to lack antecedent basis for "a zinc finger binding protein according to claim 30," because claim 30 recites a polynucleotide. In response, claim 39 has been amended to remove reference to the protein of claim 30. Accordingly, this rejection can be withdrawn. Inasmuch as claims 36, 37, 40 and 41 all depend from claim 39, withdrawal of the rejection of these claims is also in order.

Claim 10 was stated to lack antecedent basis for "the zinc finger component," because "component" is used in the singular in claim 10 and in the plural in the referenced claim. In response, claims 6, 10 and 30 have been amended so that proper antecedent basis exists for claim 10. Accordingly, this rejection of claim 10 can be withdrawn.

Claim 28 was stated to lack antecedent basis for "the third finger component." In response, claim 28 has been amended to recite a "third zinc finger component" so that the claim language is consistent with that of claim 26, from which it depends. Applicants also direct attention to the specification at page 8, lines 6-14 and page 20, lines 18-24, wherein the meaning of the term "third zinc finger" is clearly set forth.

Claimed Subject Matter

Applicants note that the term "non-C2H2 zinc finger" appears to have been interpreted by the Office to include any amino acid sequence that is not a C2H2 zinc finger (*e.g.*, Office Action at pages 11 and 13, for example). In fact, the term "non-C2H2" is intended to modify the term "zinc finger." Claim 30, as amended, explicitly recites that the claimed polynucleotides encode a protein in which at least one zinc finger component of the protein is a non-C2H2 zinc finger.

35 U.S.C. § 102 (b)

Claims 2, 4, 6, 22, 25, 27, 30, 31, 32, 36, 39, 40 and 41 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Miesfeld *et al.* as evidenced by Hard *et al.* and Schena *et al.* In summary, Miesfeld (which describes a C_4-type glucocorticoid receptor) is cited as teaching an isolated polynucleotide encoding a non-naturally-occurring zinc finger protein comprising one or more non-C_2H_2 zinc finger components. The non-C_2H_2 zinc finger components encoded by Miesfeld's polynucleotide are stated to be a hormone binding component and unspecified non-DNA binding domains. *Office Action* at page 11. The Office also states that the protein encoded by Miesfeld's polynucleotide "reads on a protein designed to bind to a target sequence because the mutant protein was designed to have the DNA-binding domain which binds to a particular sequence." *Office Action* at page 11.

The secondary references were cited as evidence that the teachings of Miesfeld inherently meet the claim limitations. It appears that Hard has been cited to support the contention that the glucocorticoid receptor contains a non-C_2H_2 zinc finger and that Schena has been cited with respect to target sequences, target cells, the length of the target site and the presence of an activation domain in a fusion polypeptide.

Applicants traverse the rejection and supporting remarks.

First, Applicants disagree with the Office's contention that the mere presence of a DNA-binding domain in a protein means that the protein has been designed or engineered to bind a target sequence. The meaning of the claim term "engineered zinc finger

protein" has been clearly set forth in the specification; *e.g.*, at page 10, lines 19-29. The protein encoded by Miesfeld's polynucleotide is simply a naturally-occurring protein that has been subjected to deletion mutagenesis. Its structure has in no way resulted from the application of either rational criteria or empirical processes for obtaining a protein that binds specifically to a target sequence. Thus, Applicants do not believe that Miesfeld's polynucleotide meets the "engineered to bind a target sequence" limitation of claim 30, either expressly or inherently.

Moreover, it is well-known to those of skill in the art that the C_4-type DNA-binding domains present in the glucocorticoid receptor, as disclosed by Miesfeld and Hard, are not zinc fingers. *See*, for example, Pabo *et al.* (1992) *Ann. Rev. Biochem.* **61:**1053-1095 (attached hereto as Exhibit A) at page 1069, wherein Dr. Pabo, a noted authority in the field of zinc finger proteins, states:

> Unfortunately, the term "zinc finger" has acquired a loose-almost topological-definition and has been used when referring to almost any sequence that has a set of cysteines and/or histidines within a short region of polypeptide chain. Here [in a section of the review entitled "Zinc Finger"] we focus on fingers that are structurally homologous to the fingers in TFIIIA. Other cysteine-rich and histidine-rich motifs, such as those that occur in the steroid receptors, in the yeast transcription factor GAL4, and in certain retroviral proteins, are discussed later in this review. (emphasis added)

Thus, the Pabo review makes clear that the C_4 DNA binding domain of the glucocorticoid receptor is not a zinc finger. Accordingly, references relating to such binding domains cannot anticipate the presently-pending claims.

Indeed, Hard *et al.*, cited by the Office as evidence that the C_4 DNA-binding domain of the glucocorticoid receptor reads on the claimed non-C_2H_2 zinc fingers, actually rebuts that assertion and is entirely consistent with Pabo's statement referenced above. For example, Hard *et al.* state (at page 157, second column), with respect to the glucocorticoid receptor DNA-binding domain:

> The presence of zinc-binding domains is reminiscent of the "zinc finger" motif found in *Xenopus* TFIIIA [reference

> omitted], as well as similar domains found in retroviral nucleic acid binding proteins [reference omitted]. However, the hormone receptor zinc-coordinating regions are not homologous to these other zinc fingers, suggesting that the DNA-binding domain of the steroid and thyroid hormone receptors constitutes a distinct structural motif. (emphasis added)

Hard *et al.*'s structural analysis of the C_4 DNA-binding domain of the glucocorticoid receptor confirms the distinctness of the structure of this domain as compared to the claimed zinc fingers. For example, Hard *et al.* identify several regions of secondary structure, within a segment of the glucocorticoid receptor containing two zinc coordinating domains, that are very different from the secondary structure of the claimed zinc finger proteins. *See* page 157, third column continuing to page 158, first column where Hard *et al.* state:

> These [secondary structure] elements include two α-helical regions encompassing Ser^{459} to Glu^{469} and Pro^{493} to Gly^{504}, a type I reverse turn between residues Arg^{479} to Cys^{482}, a Type II reverse turn between residues Leu^{475} to Gly^{478}, a short stretch of antiparallel β sheet involving residues Cys^{440} and Leu^{441} and Leu^{455} to Cys^{457}, as well as several regions of extended peptide conformation. No evidence for α-helical domains could be found within the two finger regions.

Thus, the secondary structure of the glucocorticoid receptor DNA-binding domain disclosed by Miesfeld and Hard is quite different from that of the claimed zinc finger proteins. For example, in the claimed proteins, the two amino-terminal zinc-coordinating residues are part of a β turn structure comprising two antiparallel β sheets. By contrast, antiparallel β sheet structure in the glucocorticoid receptor DNA-binding domain consists of one of the two amino-terminal zinc-coordinating residues (Cys^{440}) and one of the two carboxy-terminal zinc coordinating residues (Cys^{457}) of the first (*i.e.*, amino-terminal) zinc coordinating domain. (*See, e.g.*, Figure 1 of Hard *et al.* which discloses the zinc-coordinating residues of the glucocorticoid receptor.) The second zinc coordinating domain of the glucocorticoid receptor DNA-binding domain contains no β sheet structure at all, according to Hard.

Additionally, the α-helical portion of the claimed zinc fingers contains both of the carboxy-terminal zinc-coordinating residues and extends one residue past the second zinc coordinating residue (see the specification at page 17, line 30 through page 18, line 1). However, both α-helical regions of the glucocorticoid receptor DNA-binding domain contain only one of the two carboxy-terminal zinc-coordinating residues (Cys^{460} and Cys^{495}) and extend well past the second zinc coordinating residue into the region downstream (*i.e.*, carboxy-terminal) of the zinc coordinating domain.

Yet another structural distinction between the glucocorticoid receptor DNA-binding domain and the claimed zinc finger proteins is described by Hard *et al.* on page 159, third column: "The DBD [*i.e.*, glucocorticoid receptor DNA-binding domain] is folded into a single domain with several contacts between the two zinc finger regions, in contrast to the common view that the two zinc fingers should represent distinct subdomains." By contrast, in the claimed zinc finger proteins, individual zinc fingers bind DNA as independent domains. *See*, for example, page 17, lines 3-9 of the specification.

For the reasons noted above, one of skill in the art would not consider a glucocorticoid receptor DNA-binding domain to anticipate a zinc finger protein comprising a non-C_2H_2 zinc finger that has been designed to bind a target sequence, as claimed. Moreover, the pending claims now recite the distinctions more explicitly. Accordingly, withdrawal of the rejection is requested.

35 U.S.C. § 102 (e)

Claims 2, 4, 6, 10, 25-27, 30-32, 36 and 39-41 stand rejected over U.S. Patent No. 5,905,146. The Office states that the middle finger of the S1-3 protein disclosed in the '146 patent is a non-canonical C_2HZ zinc finger, as claimed.

In response, Applicants do not agree that the middle finger of the S1-3 protein is a non-canonical zinc finger; rather, it is a canonical C_2H_2 zinc finger. The canonical C_2H_2 formula is provided on page 7, line 10 of the specification as follows:

$(X)_3$-Cys-$(X)_{2-4}$-Cys-$(X)_{12}$-His-$(X)_{1-7}$-His-$(X)_4$

The Middle finger of the S1-3 protein, as shown in Figure 3B (b) of the '146 patent, conforms explicitly to the canonical C_2H_2 structure that is excluded from the scope of the pending claims, as follows:

$(X)_3$ = P-Y-K

C

$(X)_{2-4}$ = Q-L

C

$(X)_{12}$ = Y-Y-E-T-K-H-T-E-E-L-D-S

H

$(X)_{1-7}$ = L-R-N-E

H

$(X)_4$ = K-V-S-R

Moreover, since the disclosure of the '146 patent makes clear that S1-3 is a naturally-occurring protein, it cannot be considered to have been engineered to bind to a target sequence, as claimed. *See* also page 10, lines 19-29 of the specification and the arguments presented above. Accordingly, the rejection should be withdrawn.

35 U.S.C. § 103(a)

1. Claims 2, 4, 6, 26-28, 30-32, 36, 37 and 39-41 stand rejected as allegedly obvious over U.S. Patent No. 6,326,166 in view of Hard *et al.* The Office Action states that the '166 patent discloses a fusion protein comprising two zinc fingers and the DNA-binding domain of the glucocorticoid receptor and that Hard *et al.* teach that the glucocorticoid receptor comprises two C_4 "zinc fingers."

In response, Applicants note that, for the reasons given above regarding the rejection under 35 U.S.C. § 102(b), the C_4 binding domain of the glucocorticoid receptor does not meet the limitations of the claimed non-C_2H_2 zinc fingers. Moreover, the '166 patent's use of the C_4 DNA-binding domain teaches away from the use of non-canonical zinc fingers, as claimed. Accordingly, Applicants believe that the Office has failed to make a prima facie case of obviousness, and the rejection should be withdrawn.

2. Claims 2, 4, 6, 25-28, 30-32, 36, 37 and 39-41 stand rejected as allegedly obvious over the '166 patent in view of Hard *et al.*, as above, further in view of U.S. Patent No. 5,880,333. The '333 patent is cited as teaching the Maize C1 activation domain.

In response, Applicants note that, inasmuch as the '333 patent fails to cure the deficiencies of the primary references, the rejection is inapplicable and should be withdrawn.

CONCLUSION

Applicants believe that the pending claims are in condition for allowance and look forward to notification to that effect, as well as notification of rejoinder of generic claims and rejoinder of method claims 42-51.

Respectfully submitted,

Date: May 19, 2005

By: Sean Brennan

Sean M. Brennan
Registration No. 39,917

Sangamo BioSciences, Inc.
501 Canal Blvd., Suite A100
Richmond, California 94804

Telephone: (510) 970-6000 ext. 252
Facsimile: (510) 236-8951